REMARKS

This amendment is responsive to the Office Action mailed November 8, 2005. Claims 30, 32, 33, 35-39, 41-65 are under examination.

Claim 35, which is objected to for depending from a later introduced claim, *i.e.*, Claim 39, has been cancelled and reintroduced as new Claim 66. The claim now correctly refers to a previous claim from which it depends. No new matter is presented.

Claim 61, which recited plasmid pMEG-104 has been cancelled. Claim 62 has been amended to depend from Claim 60. No new matter is presented.

Claim 46 has been amended to correct an obvious typographical error.

Since the requested amendments relate only to requirements of the Examiner as to form, Applicant believes the amendments fall within the definition of amendments "complying with any requirements of form expressly set forth in a previous Office action" that are permissible under 37 C.F.R. §1.116, therefore entry and consideration of the amendments is respectfully requested.

Response to issues presented under 35 U.S.C. §112, first paragraph

Claims 61-64 are rejected under 35 U.S.C. §112, first paragraph, as non-enabled, i.e., containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to make and use the invention. Specifically, the Examiner objects to Claim 61, which further specifies plasmid pMEG-104, as not being supported by the specification in sufficient detail so as to be reproduced by a person skilled in the art.

Applicant disagrees; however, Applicant has cancelled Claim 61 herein. The dependencies of Claims 62-64 have been amended accordingly. Applicant submits that the rejection under 35 U.S.C. §112, first paragraph, is now moot.

Response to issues presented under the judicially-created doctrine of obviousness-type double patenting

In the Office Action, Claims 30, 32-33, 35-60, and 65 are rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 1-24 of U.S. Patent No. 6,780,405 (hereinafter "the '405 patent"). Specifically, the Examiner contends that although the claims are not identical, they are not patentably distinct, stating:

> "the allowed species of method of inducing an immunoprotective immune response in a vertebrate anticipates the instantly claimed invention of inducing any type of immune response in an animal, wherein the composition administered in the instant Application comprises a bacteria that may or may not be attenuated, but the allowed species of microorganism must be attenuated, the viability system of the instant Application may be controlled by any number o[f] regulate[]able control sequences, but the allowed method administers a species which requires specific regulatory sequences." (Office Action dated January 12, 2005, page 4.)

Applicant traverses. Obvious-type double patenting is a doctrine aimed at preventing an extension of the patent right by seeking additional patents on subject matter that differs insignificantly from a patent already obtained. The doctrine requires rejection of an application claim when the claimed subject matter is not patentably distinct from the subject matter claimed in a commonly owned patent. *In re Braat*, 937 F.2d 589, 592, 19 U.S.P.Q.2D (BNA) 1289, 1291-92 (Fed. Cir. 1991). Its purpose is to prevent an unjustified extension of the term of the right to exclude granted by a patent by allowing a second patent claiming an obvious variant of the same invention to issue to the same owner later. *In re Goodman*, 11 F.3d 1046, 1052, 29 U.S.P.Q.2D (BNA) 2010, 2015 (Fed. Cir. 1993).

The judge made law of obvious-type double patenting was developed to cover the situation where patents are not citable as a reference against each other and therefore can not be examined for compliance with the rule that only one patent is available per invention. Double patenting thus is applied when neither patent is prior art against the other. *General Foods Corp. v. Studiengesellschaft Kohle mbH*, 972 F.2d 1272, 1278-81, 23 U.S.P.Q.2D (BNA) 1839, 1843-46 (Fed. Cir. 1992) (summarizing the criteria for obviousness-type double patenting). As the court explained in *In re Boylan*,

> "it must always be carefully observed that the appellant's patent is not 'prior art' under either section 102 or section 103 of the 1952 Patent Act." 55 C.C.P.A. 1041, 392 F.2d 1017, 1018 n.1, 157 U.S.P.Q. (BNA) 370, 371 n.1 (CCPA 1968).

Analysis

An obvious-type double patenting analysis entails two steps. First, the Examiner must construe the claims in the earlier patent and the claims in the later patent and determine the differences. MPEP §804; *Georgia-Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1326, 52 U.S.P.Q.2D (BNA) 1590, 1593 (Fed. Cir. 1999). Second, the Examiner must determine whether the differences in subject

matter between the two claims render the claims patentably distinct. MPEP §804; *Id. at 1327, 52 U.S.P.Q.2D (BNA) at 1595.*

Since the doctrine of double patenting seeks to avoid unjustly extending patent rights at the expense of the public, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis. MPEP §804.

A comparison of the independent claims of the present invention and US Patent No. 6,780,405 is set forth below:

US Application No. 09/120,970	**US Patent No. 6,780,405**
1. A method for inducing an immune response in a warm-blooded animal comprising administering to the animal a composition comprising a bacterial cell, wherein	1. A microorganism comprising a regulated antigen delivery system (RADS), wherein the RADS comprises
(a) the bacterial cell comprises an expression gene that encodes an antigen, and an Environmentally Limited Viability System,	(a) a vector comprising
(b) the antigen is introduced into the animal,	(1) a gene encoding a desired product inserted into a site for insertion of a gene encoding a desired gene product, wherein the gene encoding the desired gene product is operably linked to a second control sequence;
(c) **the bacterial cell is viable when in the animal and non-viable when outside of the animal**, and	(2) a first origin of replication (ori) conferring vector replication using DNA polymerase III; and
(d) the Environmentally Limited Viability System comprises **an essential gene that is under the control of an environmentally regulatable control sequence**, wherein	(3) a second ori conferring vector replication using DNA polymerase I,
(i) expression of the essential gene in the cell is essential to the viability of the cell,	wherein the second ori is operably linked to a first control sequence repressible by a first repressor, and wherein the runaway vector does not comprise a phage lysis gene; and
(ii) **the essential gene is expressed when the cell is in the animal and is not expressed when the cell is outside of the animal**,	(b) a gene encoding a first repressor operably linked to a first activatible control sequence.
(iii) the essential gene is essential for metabolism, growth, cell wall integrity or cell membrane integrity of the bacterial cell, and	
(iv) the essential gene is a copy of a native chromosomal gene wherein the chromosomal copy of said native gene is inoperable.	

It is clear that the claims of the present application are quite distinguishable from the claims of the '405 patent and are patentably distinct. The present invention and claims are directed to environmentally limited viability systems (ELVS) for microbes based on differences in environmental conditions, i.e., permissive and non-permissive environments. Viability of the microorganisms is limited to the permissive environment by specifically expressing one or more essential genes while only in the permissive environment, and/or expressing one or more lethal genes only in the non-permissive environment. One of the objects of the present invention was to develop an alternative biological containment system specifically suited for vaccine use, *i.e.*, an alternative to biological containment systems in which a suicide gene, that is, a gene that *actively* kills the microorganism, is the primary containment option. The complexity and high selective pressure to develop an inactivating mutation in the killing gene (or its regulators) make "lethal gene only" containment systems impractical, particularly for the vaccine field. Applicant has designed a novel alternative that avoids the problems associated with the actively lethal systems by providing a containment system that regulates an essential gene, *i.e.*, a gene or gene product that is essential for metabolism, growth, cell wall integrity, or cell membrane integrity. By use of the regulation methods described in Applicant's specification, the essential gene can be regulated to be only transcribed/expressed in a permissive environment.

In contrast, the '405 patent **claims** are directed to regulated antigen delivery systems (RADS) utilizing microorganisms containing a dual-*ori* (one low copy, one high copy) runaway vector (RAV) and at least one chromosome-encoded regulated repressor, in which the copy number of the RAV increases in response to reduced levels of the repressor responsible for repression of the high copy number *ori* of the vector. In operation, the RAD system allows for the foreign gene to be stably maintained on the plasmid at a low copy number, which is optimal during growing conditions (such as in a fermenter). Under desired conditions such as upon inoculation, however, the vector is activated into a "runaway" state by regulated de-repression of the high copy number *ori* and de-repression of foreign gene expression.

The object of the '405 patent is to design a system that produces (*i.e.*, by runaway expression) and releases large amounts of antigen at a desired time, e.g., after inoculation.

It is clear that the claims of the present application and of the reference patent are readily distinguishable and not obvious variants over one another. The present claims, *inter alia*, call for:

- a gene essential for metabolism, growth, cell wall integrity or cell membrane integrity of the bacterial that is under the control of an environmentally regulatable control sequence; and
- the essential gene is expressed when the cell is in the animal and is not expressed when the cell is outside of the animal, which renders the bacterial cell viable when in the animal and non-viable when outside of the animal

The **claims** of the '405 patent call for:

- a regulated antigen delivery systems utilizing microorganisms containing a dual-*ori* (one low copy, one high copy) runaway vector and at least one chromosome-encoded regulated repressor

Applicant notes that the Examiner cites passages of Applicant's specification in support for her contention that the claims are obvious variants over the claims of the '405 patent. However, Applicant points out that the focus of any double patenting analysis necessarily is on the claims in the patents or patent applications involved in the analysis. As the CAFC has stated regarding obvious-type double patenting:

> "Under that facet of the doctrine of double panting, we must direct our inquiry to whether the claimed invention in the application for the second patent would have been obvious from **the subject matter *of the claims* in the first patent**, in light of the prior art." *In re Longi,* 225 USPQ 645, 648 (Fed. Cir. 1985) (citing *Carman Industries Inc. v. Wahl,* 220 USPQ 481, 487 (Fed. Cir. 1983)) (emphasis added).
>
> ***
>
> "When considering whether the invention defined in a claim of an application [would have been] an obvious variation of the invention defined in the claim of a patent, **the disclosure of the patent may not be used as prior art**." *General Foods Corp. v. Studiengesellschaft Kohle mbH,* 972 F.2d 1272, 1279, 23 U.S.P.Q.2d 1839, 1846 (Fed. Cir. 1992); MPEP §804(II)(B)(1).

While the Examiner is not totally precluded from referencing the specification, those situations are limited to definitions in the specification (to be used as a dictionary to determine the meaning of an ambiguous claim term) and "those portions of the specification which provide support for the patent claims." MPEP §804(II)(B)(1).

Applicant notes that the Examiner's primary basis for the obvious-type double patenting rejection concerns a discussion in the '405 ***specification*** regarding the Regulated Antigen Delivery system having an inherent containment system.

Foremost, Applicant notes that this is an improper reference to the specification – there is no reference to a containment system in the claims of the '405 patent requiring reference to the specification for definition or even support. Applicant reminds the Examiner that the **disclosure of the patent may not be used as prior art** and that the patent is not prior art against the present application. Once again, since the doctrine of double patenting seeks to avoid unjustly extending claimed patent rights at the

expense of the public, the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis. MPEP §804.

Moreover, Applicants note that "containment system" cursorily mentioned in the '405 specification (and absent in the claims) functions through *an entirely different* mechanism. In the RADS system of the '405 patent, a gene encoding a desired gene product is placed on a runaway vector which, under repressed conditions, does not express foreign gene product and is maintained at low copy number. When the repression of the second ori and the second repressible control sequence is removed, the runaway vector is now "under derepressed runaway conditions", and both the copy number of the vector and the expression of the desired (foreign) gene product increase dramatically. The high copy number replication of the vector and the high expression of a foreign gene eventually overwhelm the host microorganism: the energy requirements of high copy replication and high foreign gene expression drain the cell and interfere with production of native proteins required to maintain the viability of the cell. The cell growth rate lowers under the burden of replicating the runaway vector and overexpressing the foreign gene product, and the host cell becomes vulnerable to other factors (such as immune attack). This indirect containment feature is, however, secondary to the technical advantage of having high foreign gene product expression occur at the most desirable point.

Accordingly, even if a containment system was recited in the '405 patent claims, which it is not, Applicant points out that the claims would *still be* patentably distinct because the *indirect* containment system described in the '405 specification (energy limitation) is wholly unrelated to the *direct* containment system of the present ELVS claims, wherein expression of a gene essential to the viability of the cell is ceased and, optionally, an actively lethal gene is expressed, when the microorganism is outside the host mammal.

The only similarity between the two sets of claims is that they both contemplate utilizing environmentally regulatable control sequences, for example, *araC*P_{BAD}. However, the present claims contemplate use of such sequences to control the expression of a gene essential to the viability of the cell, thus creating an environmentally limited viability. In contrast, the claims of the '405 patent contemplate the use of such control sequences for controlling the expression of repressors, which in turn control the replication of the dual-*ori* runaway expression plasmid, which in turn drives expression of the foreign antigen.

The Examiner attempts to link this one common element between the two cases:

> "The microorganism of allowed claim 7 of the '405 is defined to comprise not only the RAD/RAV system, but also to comprise the ELVS system and is administered in the method of allowed claim 24.

> Therefore, the allowed claim 24 of the '405 is directed to a species which utilizes a specific environmentally regulatable control sequence, specifically araCPbad. The allowed species anticipates the instantly claimed genus of method now claimed." (Office Action dated November 8, 2006, page 5.)

Applicant notes the claims of the '405 do not "anticipate" the present invention as suggested. The claims of the '405 patent do not cover an ELVS wherein viability of the cell is controlled by the environmentally controlled expression of a gene essential for metabolism, growth, cell wall integrity or cell membrane integrity of the bacterial cell. Nor is an "anticipation" analysis applicable in an obvious-type double patenting rejection. Moreover, this statement is *factually* incorrect. Claim 7 of the '405 patent actually recites:

> 7. The microorganism of Claim 5, wherein the first activatable control sequence is *araC*P_{BAD}.

Following the thread of dependency to Claim 1 of the '405 patent reveals that said "first activatible control sequence" is found in step (b), which recites:

> "(b) a gene encoding **a first repressor** operably linked to a *first activatible control sequence*."

In the '405 patent antigen delivery system, the first repressor functions to repress the second origin of replication on the runaway expression plasmid, not, as the Examiner states, to function as the ELV system recited in the present claims. There is no regulated expression of an essential gene ELV system in the claims of the '405 patent.

Accordingly, since the methods of the present invention contain components and advantages not taught or suggested by the claims of the '405 patent, the present claims are NOT obvious variants of the prior patented claims and Applicant respectfully requests reconsideration and withdrawal of the rejection under the judicially created doctrine of obvious-type double patenting.

In view of the foregoing remarks, reconsideration and allowance of the claims as amended are respectfully requested.

Respectfully submitted,

Leon R. Yankwich, Registration No. 30,237
Michael R. Wesolowski, Registration No. 50,944
Attorneys for Applicant
YANKWICH & ASSOCIATES , P.C.
201 Broadway
Cambridge, Massachusetts 02139
telephone: 617-374-3700
telecopier: 617-374-0055

Certificate of Mailing

The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service under 37 CFR 1.8, postage prepaid, in an envelope addressed to: Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date indicated below.

April 10, 2006
date

Michael Wesolowski, Reg. No. 50,944